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**Case Report**

# A Rare Presentation of HIST1H1E Syndrome with Short Stature and Multiple Pituitary Hormone Deficiencies



İlayda Altun, Elvan Bayramoğlu, Hasan Karakaş, Gökçe Velioğlu Haşlak, Mert Uçar, Hande Turan, Olcay Evliyaoğlu
Pediatric Endocrinology, Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul,Turkey

**Abstract**
HIST1H1E Syndrome is a rare autosomal dominant disorder resulting from a heterozygous variation in the H1-4 gene located on chromosome 6p22.2. Mental retardation, recognizable facial features, skeletal abnormalities and overgrowth are the main clinical manifestations of this syndrome. A 17-year-old male presented to the pediatric endocrinology clinic due to short stature. He had a characteristic facial appearance with neurodevelopmental delay. Genetic analysis revealed a heterozygous pathogenic variation in the H1-4 gene located on chromosome 6p22.2 which confirmed his diagnosis of HIST1H1E syndrome. In our case, distinguished by the co-occurrence of short stature and obesity accompanying central hypothyroidism and growth hormone (GH) deficiency due to hipoplastic pituitary gland, which differs from the somatic overgrowth characterizing this syndrome.These is the second reported HIST1H1E syndrome case with hyposecretion of multiple pituitary hormones caused by hypoplasia in the pituitary gland.
**Keywords:** Central hypothyroidism, Growth hormone deficiency, Hipoplastic pituitary gland, HIST1H1E, Short stature

Ilayda Altun, MD, Pediatric Endocrinology, Istanbul University Cerrahpasa, Cerrahpasa Medical Faculty, Istanbul,Turkey
ilaydaauslu@gmail.com
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**Introduction**
Histones play a key role in dynamic packaging of nuclear DNA in chromatin, epigenetic modifications and the regulation of chromosome structure (1). Histone Gene Cluster 1 Member E, HIST1H1E, located at chromosome 6p22.2, a member of the H1 gene family, encodes Histone H1.4, responsible for higher order chromatin structure. HIST1H1E syndrome (also known as Rahman syndrome, OMIM #617537) was first described as autosomal dominant intellectual disability (ID) syndrome is associated with pathogenic frameshift variations in the C-terminal domain of the H1-4 gene. It has been associated with a distinctive facial features(2) (micrognathia, deep-set eyes, down-slanting palpebral fissures high hairline, hypertelorism, telecanthus), hypotonia, behavioral issues and mental problems (combinations of obsessive behaviors, anxiety/phobias, autistic spectrum disorder/traits, attention-deficit/hyperactivity disorder and others), cardiac and skeletal abnormality, cryptorchidism, abnormal dentition including dental erosions, thin enamel, crumbling teeth, and multiple dental caries, ectodermal abnormalities and hypothyroidism (3). Autism spectrum disorder and ıntellectual disability has been described as a component of the presentation in a patient with HIST1H1E syndrome (4).
HIST1H1E syndrome also serves as a mnemonic form for some of key features of the syndrome: H for hypotonia, I for intellectual disability, S for skeletal abnormalities, T for testicular and thyroid anomalies, H for heart anomalies and E for ectodermal features.
Since the HIST1H1E syndrome was first described as overgrowth syndrome, Takenouchi et al. suggested that overgrowth is not hallmark clinical feature of HIST1H1E syndrome (5) Few case reports evaluating growth patterns in Rahman syndrome have also focused on height variability. We report a case of HIST1H1E syndrome in a patient with obesity, short stature and deficiency in multiple pituitary hormones.

**Case Report**
The male proband is the first child of his healthy, consanguineous Turkish parents. He was born at 38 wk, with a weight of 2,600 g (-1.78 SD) and a length of 48.0 cm (-0.91 SD). Anthropometric measurements was appropriate for the gestational age. He stayed in the neonatal intensive care unit for a month due to hypotonia and respiratory distress. Cardiologic problems including secundum atrial septal defect, patent ductus arteriosus were detected in neonatal period. He was able to sit without support at the age of 1 year. He attained independent walking by the age of 2 years, and began to produce phrase-level speech following the age of 3 years. Cryptorchidism was detected and he had bilateral orchiopexy at 2 years of age. At 3 years of age, his weight was 20 kg (+2.08 SD), height 104 cm (+1.81 SD).
The patient demonstrated intellectual disability and neuromotor developmental delay . He had a history of afebrile seizure at the age of 9. Brain Magnetic Resonance Imaging (MRI) performed showed focal hypoplastic corpus callosum. At the age of 17, the same patient was referred to our tertiary pediatric endocrinology center with obesity and short stature. His body mass index (BMI) was 34.5 kg/m2, his weigth was 87.6 kg (1.48 SD); his height was 159.4 (-2.53 SD). His pubertal development was appropriate to his chronological age. He had a characteristic facial appearance with bitemporal narrowing, a high hairline ,deep set eyes, hypertelorism and downslanting palpebral fissures. Additionally he showed abnormal dentition problems including dental erosions,crumbling teeth, thin enamel and multiple dental caries; ectodermal issues (including thin nails, sparse hair and hyperkerotosis); Informed consent was obtained from his parents and himself for publication of an image of the patient's face (shown in Fig. 1). Skeletal anomalies included kyphoscoliosis and hallux deformity. The patient demonstrated a modarate intellectual disability.
In the routine laboratory examination performed for the short stature of the patient, thyroid function tests were found to be compatible with central hypothyroidism (free thyroxine (fT4): 0.75 ng/dL (0.98-1.63ng/dL), triiodothyronine(fT3): 2.67 ng/ dL (2.56-5.01), thyroid-stimulating hormone (TSH): 3.2 mIU/L (0.51-4.3) and Insulin- like growth factor-1 (IGF 1: 92 ng/mL;-2.91SD) levels were found to be low. In the evaluation of other anterior pituitary hormones; adrenocorticotropic hormone (ACTH: 38.3 pg/mL (0-46), cortisol (14.4 µg/dL (6.2-19.4), prolactine (13,2 µg/l ) levels were normal. Gonadotropin (LH: 8.96mU/mL, FSH: 10.2 mU/ml) levels are at the upper limit of the reference range but total testesterone levels (265 ng/dl) are not comptiable with hyogonadism. Hypothyroidism was managed with levothyroxine 50 µg. Growth hormone (GH) deficiency was demonstrated in the GH stimulation test performed after euthyroidism was achieved (peak GH in an L-Dopa stimulation test, 2.51ng/mL; peak GH in an clonidine stimulation test 1.53 ng/mL). Wrist X-ray reported normal bone age consistent with the chronological age of the patient at the age of 17. GH stimulation testing served a diagnostic rather than therapeutic purpose as part of adult endocrine evaluation because growth plates have closed. We explained test's purpose and clinical utility to our patient and his family before proceeding. A brain and sellar MRI showed pituitary hypoplasia. On the basis of these findings, the patient was diagnosed with central hypothyroidism and GH deficiency. Bone mineral density was measured at 1.11 g/cm³, which is within the normal range.

In the laboratory examination for obesity; high fasting glucose (105 mg/dl) and concurrent insülin (13.4 microU/ml), c peptide (2.72 ng/ml), homa-ır (3.5) and HbA1C (28.96 mmol/mol/ 4.8%) levels were found. Impaired glucose tolerance was demonstrated on glucose tolerance test (1 hour postprandial level of 168 mg/dl and a 2-- hour postprandial level of >140 mg/dl). Total cholesterol was 216.8 mg/dl with triglyceride 252mg/dl, LDL 147 and HDL 30.4 mg/dl. Grade 2 fatty liver disease was detected by abdominal ultrasound. The patient was treated with metformin.

Conventional G-banding cytogenetic analysis demonstrated a normal karyotype of 46,XY. Our patient underwent whole exome sequencing (WES) incorporating copy number variant (CNV) analysis. WES was performed using the Roche KAPA HyperExome capture kit and sequenced on the Illumina NovaSeq 6000 platform. Library preparation was conducted according to the manufacturer's protocols. Detected variant were annotated and interpreted using multiple population and disease databases, including ClinVar, OMIM, PubMed, and in silico tools. For pathogenicity classification, we utilized Illumina BaseSpace Variant Interpreter, InterVar, VarSome, Franklin by Genoox, and other relevant resources, following the 2015 ACMG-AMP guidelines. A de novo pathogenic frameshift variant in the H1-4 gene: c.430dupG; p.(Ala144Glyfs*52) (OMIM 142220, NM_005321.3), located on chromosome 6p22.2 as pathogenic based on ACMG criteria was identified. The analysis was guided by Human Phenotype Ontology (HPO) terms including short stature (HP:0004322), panhypopituitarism (HP:0000829), obesity (HP:0001513), and intellectual disability (HP:0001249).

**Discussion**

Although HIST1H1E syndrome was initially reported in 2017 as presenting with overgrowth and intellectual disability, recent studies suggest that overgrowth may not be a hallmark feature of that syndrome (4). In the present report, we present a case with a de novo truncating variant of the HIST1H1E gene, exhibiting intellectual disability and the characteristic facial and skeletal features of HIST1H1E syndrome. However, in contrast to the typical presentation, the patient displayed marked decreased height over time and eventually short stature. Further investigation into the etiology of the short stature revealed multiple pituitary hormone deficiencies. Moreover, the patient also presented with obesity and impaired glucose tolerance. These findings that suggest the clinical heterogeneity of the syndrome may be broader than previously reported in the literature.

Zhao et al. (3) reported article that genotype–phenotype relationships were systematically reviewed based on data from a relatively large 52 patient cohorts with HIST1H1E, 23 frameshift variants. His findings revealed that likely gene-disrupting variants in HIST1H1E contribute to phenotypic heterogeneity. Variants in HIST1H1E have been frequently associated with a specific subtype of neurodevelopmental disorders. Although the phenotypes of patients are complex, some clinic presentation that are common to most patients are observed inclued developmental delay(50/52), prominent forehead (40/52), high hairline (45/52), downward slant palpebral fissures (35/52), hypertelorism (37/52), cryptorchidism (17/25) similar to our pateint's clinic problems. 430 dupG;_p.(Ala144Glyfs*52) variant was most commonly detected in his study same as our case's variation.

Height SD range of patients with Ala144 frameshift variants had detected between -1.74 SD - +3.65 SD. We want to focus on height variability that ın our case, distinguished by the co-occurrence of short stature with height $\leq -2$ SD compared to the cases reported in the literatüre. Tanabe et al. also reported one case that had short stature with $\leq -2$ SD(6).

Endocrinologic problems included hypotyroidim were reported by different case reports. To date, hypothyroidism has been reported as an endocrinological problem without differential diagnosis between central hypothyroidism and primary hypothyroidism. Burkardt et al. reported 30 unrelated individuals with frameshift HIST1H1E variants. Twelve of them had 430 dupG; p.(Ala144Glyfs*52) variant which was the same variation found in our case. From the 30 patients , 25% patients were reported with hypothroidism (7).

Zhao et al. (3)(3) reported 4(4/52) unrelated individuals diagnosed as HIST1H1E syndrome who had hypothyroidism and 2 of them had 430 dupG;_p.(Ala144Glyfs*52) variant.

Burkardt et al. (7) and Zhao et al. (8) reported highly varied brain MRI findings. Hypoplastic corpus callosum, ventriculomegaly, small posterior fossa, partial decent of cerebellar tonsils were the common MRI findings. Pituitary hypoplasia has been reported in one case who had de novo, c.360_361insA, p.(Ala123Glyfs*73) variation associated with hypothyroidism (3,7).

Tanabe et al reported first case of HIST1H1E syndrome with hyposecretion of multiple pituitary hormones involving central hypothroidism, GH deficiency and hypogonadotropic hypogonadism(6). The second case of HIST1H1E syndrome with a short stature and deficiency in several pituitary hormones (central hypothroidysm and GH deficiency).

Our Patient's height sds was high in the begining, short stature developed later on. In the literature, there are cases where the birth length is normal, but there is a loss of height later in life (3). Although the mechanism for the development of short stature has not been clarified in the literature, in our case, it is thought that short stature developed due to central hypothyroidism and GH deficiency.

Given that the FSH and LH levels of our patient are at the upper limit of the reference range(10) according to pubertal levels, the patient should be monitored for potential development of hypergonadotropic hypogonadism, as this may reflect an early compensatory response to declining testicular function Although hypogonadotropic hypogonadism has been reported in association with this syndrome in the literatüre(6) , to date, there have been no documented cases of hypergonadotropic hypogonadism.

Although obesity is not the main component of theAla144 frameshift variants, presented case was obese, with impaired glucose tolerance in 75 gr oral glucose tolerance test assoicated with hypercholesterolemia. Ahmad et al reported first case of HIST1H1E syndrome with raised BMI SD and diabetes mellitus (11). Weight SD range of patients with Ala144 frameshift variants reported by Zhao et al. were between -0.88SD - +3.3SD (3) . A raised BMI which may increase the risk of glucose metabolism problems with hypercholesterolemia.

H1.4 is a structural part of chromatin to control DNA compaction, DNA replication, recombination, repair and gene expression regulation. We would like to emphasize that the dysfunctional or abnormal conditions of H1-4 gene may cause neurodevelopmental dysfunction, due to the important structural and regulatory roles of histones. H1-4 pathogenic frameshift c430. Dup; p.(Ala144glyfs*52) may cause defects in pituitary gland organogenesis. In recent years, genome-wide methylation array analysis has allowed researchers to detect and investigate epigenetic features of diseases. Ciolfi et al. detected that a relevant proportion
of the genes containing hypomethylated regions in HIST1H1E variants are predominantly expressed in brain and encode different subunits essential for synaptic function synaptic plasticity, cognitive function. HIST1H1E-mediated regulation of chromatin compaction may contribute to neurogenesis defects (12). The studying site-specific functions of variants needed to clarify the connection between histone proteins and pituitary gland development.

**Conclusıon**

HIST1H1E gene-related disorder is a neurodevelopmental syndrome which may be recognizable through facial features. The present phenotypic feature facilitate current
knowledge regarding the spectrum of HIST1H1E variants but skeletal overgrowth should not be an essential feature. It may present with short stature which progressed in time. Multiple pituitary hormones deficiency should be kept in mind in H1-4 pathogenic frameshift variation. Additional investigations are required to elucidate the biological mechanisms underlying the frameshift variants of HIST1H1E.

**Ethıcal**

**Informed Consent**

Informed consent was taken from the parents of patient for publication. Consent was obtained from the parents for publication of an image of the patient's image.

**AUTHOR CONTRIBUTIONS**

Conceptualization and design: Ilayda Altun, Elvan Bayramoglu,Olcay Evliyaoglu. Analysis and interpretation of data: *Ilayda Altun, Hande Turan, Hasan Karakas, Mert Ucar, Gokce Velioglu Haslak, Elvan Bayramoglu, Olcay Evliyaoglu*. Drafting of the article: Ilayda Altun, Elvan Bayramoglu, Olcay Evliyaoglu. Study supervision: Olcay Evliyaoglu.

**CONFLICT OF INTEREST**

The authors declare no potential conflict of interest.

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**DATA AVAİLABİLİTY**

The datasets generated and analyzed during this studyare available from the corresponding author on reasonable request.

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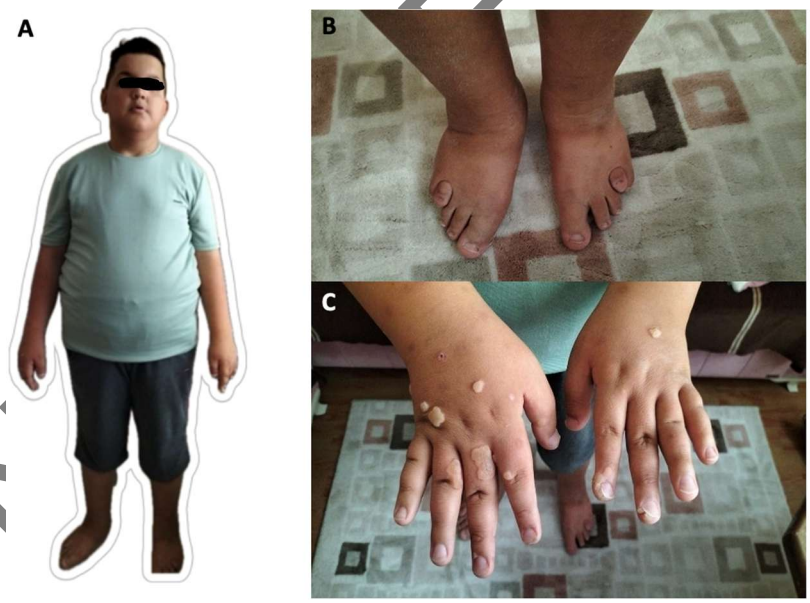
**Figure 1:**




A: Distinctive external features including characteristic facial appearance, obesity,short stature
B: Skeletal anomalies including hallux deformity.
C: Ectodermal issues including hyperkeratosis.